

## REMARKS

Claim 15 was canceled without prejudice.

The Summary of the Invention, paragraph 32, and claims 1, 2, 14, and 26 of the captioned application were amended to expressly provide the quotient of the ratio of simethicone to adsorbent. Support for this amendment can be found throughout the specification at, for example, the original Summary of the Invention, paragraph 32, and claims 1, 2, 14, and 26.

Paragraphs 16 and 17 and claims 5 and 17 were amended to correct the spelling of famotidine. The Summary of the Invention, paragraph 26, and claims 1 and 3 were amended to correct the spelling of adsorbent. Paragraph 17 was also amended to correct the spelling of thereof. The claim dependency of claim 9 was changed to recite claim 3 to provide express antecedent basis for the adsorbents listed therein. Claims 23 and 24 were amended to correct antecedent basis for the term "composition" by, amongst other things, inserting the term "compressed admixture" therefor. Finally, claim 26 was amended to delete the term adsorbent and inserting the terms silicified microcrystalline cellulose and magnesium aluminometasilicate therefor.

It is submitted that no new matter has been introduced by the foregoing amendments. Approval and entry of the amendments is respectfully solicited.

### Restriction Requirement

On page 2, line 5, of the October 3, 2002 Office Action ("OA"), the Examiner required an election of a single disclosed species under 35 USC § 121 for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held allowable. The Examiner memorialized the telephonic conversation wherein the undersigned made a provisional election of famotidine as the elected species. (OA at 3.)

Such provisional election is NOT affirmed. Rather, an election of loperamide is hereby made. The Examiner is asked to remove the withdrawal of claims 6 and 18 as being drawn to a non-elected invention.

### Objection

The abstract of the disclose was objected to because of a "typographical error such as 'famotadine' [was] present in page 7, line 16." (OA at 3.) The Examiner requested correction of "famotadine" with "famotidine." *Id.*

At the outset, it is not seen where the term “famotadine” appears in the abstract of the disclosure. The Examiner is asked to confirm this understanding in the next paper issued in the captioned application. However, the term “adsorbant” as changed to “adsorbent” in the abstract of the disclosure, as well as in the Summary of the Invention and paragraph 32. Additionally, the term “famotadine” was changed to “fomatidine” in paragraphs 16 and 17. Further, the term “thereof” was corrected to “thereof” in paragraph 17.

It is believed that these spelling corrections render the objection to the specification moot and withdrawal thereof is respectfully solicited.

Claims 5 and 17 were objected to for containing the term “famotadine.” (OA at 3.) The Examiner required correction of “famotadine” with “fomatidine.” *Id.* As noted above, claims 5 and 17 have been amended to remedy the spelling error and, it is submitted, the objection is rendered moot and should be withdrawn.

Claims 1-3, 14-15, and 26 were objected to for containing the term “adsorbant.” (OA at 3.) The Examiner required correction of “adsorbant” with “adsobent.” *Id.* At the outset, it is not see where in claim 14 the term “adsorbant” is found. The Examiner is asked to clarify this in the next paper issued in the captioned application. As noted above, claims 1-3, and 26 were amended to remedy the spelling error and, it is submitted, the objection is rendered moot and should be withdrawn.

#### **Indefiniteness Rejection**

Claims 9-10, 14-15, 23-24, and 26 were rejected under 35 USC §112, second paragraph. (OA at 4.)

In making the rejection of claim 9, the Examiner asserted that “[c]laim 9 lacks antecedent basis for the term “silicified microcrystalline cellulose ” and .”magnesium aluminometasilicate” in claim 1.” (*Id.*) The Examiner further rejected claim 10, as being dependent on a rejected claim.

As noted above, claim 9 was amended to change the claim dependency from claim 1 to claim 3 to remedy the error in antecedent basis and, it is submitted, the rejection is rendered moot and should be withdrawn.

In making the rejection of claims 14-15, the Examiner asserted that “[c]laims 14-15 recites the limitation “adsorbent” or “adsorbant” in claim 13.” (*Id.*) The Examiner

asserted that there is insufficient antecedent basis for this limitation in the claim. The Examiner further rejected claim 26, as lacking antecedent basis for term “adsorbent.”

As noted above, claim 15 has been canceled without prejudice. The term “adsorbent” in claim 14 was changed to “silicified microcrystalline cellulose and magnesium aluminometasilicate.” Claim 26 was amended to remedy the spelling error in the term “adsorbent” and, it is submitted, the rejection is rendered moot and should be withdrawn.

In making the rejection of claims 23-24, the Examiner asserted that “[c]laims 23-24 lack antecedent basis for the term “the composition.” Claims 23 and 24 have been amended to included, among other things, the term “compressed admixture” as found in claim 13, from which claims 23 and 24 depend. It is submitted that the rejection is rendered moot and should be withdrawn.

#### **Anticipation Rejection**

Claims 1-2 and 4-5 were rejected under 35 USC §102(b) as anticipated by Stevens, US Patent No. 5,679,376, (“Stevens”). (OA at 5.)

For the reasons set forth below, the rejection, respectfully is traversed.

Stevens discloses

**A solid oral dosage form for the treatment of gastrointestinal disorders comprising a therapeutically effective amount of a pharmaceutical suitable for the treatment of gastric disorders selected from the group consisting of cimetidine, ranitidine, famotidine, diphenoxylate, loperamide, loperamide-N-oxide, pharmaceutically acceptable salts thereof and combinations thereof; and a therapeutically effective amount of simethicone wherein the pharmaceutical and simethicone**

(Abstract)

FIG. 6 provides dissolution profiles for three formulations of uncoated loperamide present with simethicone provided in an admixed single solid oral dosage form. The solid line indicates the dissolution profile of loperamide from a solid dosage form comprised of Simethicone GS-J (40% simethicone adsorbed onto a diluent) and uncoated granules containing loperamide. The dashed line indicates the dissolution profile of loperamide from a second solid dosage form containing granules of Simethicone GS-J (40% simethicone adsorbed onto a diluent) and uncoated granules containing loperamide. The dotted line indicates the dissolution profile of loperamide from a third solid dosage form containing granules of Simethicone GS-J (40% simethicone adsorbed onto a diluent) and uncoated granules containing loperamide. The formulations for these solid dosage forms are contained in Example 1.

(Col. 2, Ins. 40-55.)

The simethicone used in the present invention can be Simethicone USP or a commercially prepared granulation such as Simethicone GS (30% Simethicone USP adsorbed onto maltodextrins available from Union Carbide) or Simethicone GS-J (40% Simethicone USP adsorbed onto maltodextrins available from Union Carbide). The amount of simethicone contained in the solid dosage form should be sufficient to provide a therapeutic dosage to a patient suffering from gas or diarrhea and its associated symptoms. The preferred dosage ranges for simethicone is in the range of about 20 mg to about 125 mg per dosage unit, generally not to exceed 500 mg/day. The dosage ranges may vary for age and weight of a patient as well as the severity of symptoms. (Col. 4, Ins. 31-43.)

| Ingredient                     | Mg/Tablet |
|--------------------------------|-----------|
| Simethicone, USP               | 125.0     |
| Dibasic Calcium Phosphate, USP | 370.0     |
| Microcrystalline Cellulose, NF | 265.5     |
| Colloidal Silicon Dioxide, NF  | 31.5      |
| Sodium Starch Glycolate, NF    | 72.0      |
| Croscarmellose Sodium, NF      | 36.0      |
| Loperamide HCl, USP            | 2.0       |
| Total                          | 902.0     |

**DIRECTIONS:**

The third experimental tablet was manufactured in the following manner:

1. Mix loperamide HCl, dibasic calcium phosphate and microcrystalline cellulose in a planetary mixer (Hobart mixer) for 30 seconds.
2. Granulate by adding simethicone into Step 1 for 1 minute.
3. While mixing add colloidal silicon dioxide to Step 2 for 2.5 minutes.
4. Add sodium starch glycolate and croscarmellose sodium and mix for 1 minute.
5. Compress the tablets as set forth above for the first experimental tablet.

FIG. 5 shows the dissolution profile of simethicone and loperamide when provided in separate solid oral dosage form. As is shown in FIG. 6, the dissolution profile of loperamide in tablets containing both loperamide and simethicone in a single solid oral dosage form was reduced to the point that almost no loperamide was detected. The solid, dashed and dotted lines in FIG. 6 represent the dissolution profiles for the first, second and third experimental tablets, respectively. These results demonstrate the need for a new solid oral dosage form containing a combination of simethicone and a pharmaceutical suitable for the treatment of a gastric disorders.

In making the rejection, the Examiner contended only that "Stevens teaches a solid oral dosage form comprising loperamide, simethicone, microcrystalline cellulose and colloidal silicone dioxide, wherein a ratio of simethicone and microcrystalline cellulose is about 1.2.12 (125 mg :265.5 mg) or a ratio of simethicone and a combination

of colloidal silicon dioxide and microcrystalline cellulose is about 1:2.37 (125 mg:297 mg). (OA at 5.) The Examiner appears to have taken official notice that the use of microcrystalline cellulose and colloidal silicon dioxide were inherently adsorbents. Further, the Examiner concluded that since the calculated ratio of 1:2.12 (simethicone to microcrystalline cellulose) or 1 2.37 (simethicone to the combination of microcrystalline cellulose and colloidal silicon dioxide) fell within the claimed ration of simethicone to adsorbent of at least about 1:2.22 (claim 1) and at least 1:2. (*Id.*)

As is well settled, anticipation requires “identity of invention.” Each and every element recited in a claim must be found in a single prior art reference and arranged as in the claim.

We note that the Examiner asserted that dibasic calcium phosphate “falls within the broadly defined adsorbent.” (OA at 6-7.) The example relied upon by the Examiner in the instant rejection discloses using 370 mg of dibasic calcium phosphate, USP. It appears that the Examiner may have overlooked this fact in making the instant rejection.

The claimed ratios of simethicone to adsorbent were converted to their quotients in an attempt to aid the Examiner in understanding the instant invention. Using this ratio, it is clear that Stevens does not disclose as much as the Examiner asserted. For example, looking at the sole example in Stevens relied on by the Examiner provides factual evidence that the ratio of simethicone to adsorbent (dibasic calcium phosphate + microcrystalline cellulose + colloidal silicon dioxide) is 125:667, which is about 0.19. It is submitted that a ratio of about 0.19 does not fall within the claimed ratio of at least about 0.45. For this reason, the rejection is improper and should be withdrawn.

Because claims 2, 4, and 5 depend from claim 1, the rejection to these claims based on Stevens is also improper and should be withdrawn.

Claims 1-2, 4-5. 7-8, and 11-12 were rejected under 35 USC §102(b) as anticipated by Luber et al., US Patent No. 6,103,260, (“Luber”). (OA at 6.)

For the reasons set forth below, the rejection respectfully is traversed.

Luber discloses

In accordance with the present invention, the simethicone is admixed with the granulated anhydrous tribasic or dibasic calcium phosphate to form a uniform free flowing granular composition. Generally, it is desired that the admixture contain a proportionate amount of the simethicone antifoam agent and granular anhydrous calcium phosphate which is consistent with forming a free-flowing granular composition. Preferably, the proportionate amounts of the ingredients of the granular admixture composition is about 10-70% w/w simethicone and about 30-90% w/w granular anhydrous tribasic or dibasic calcium phosphate. The ingredients

(Col. 3, Ins. 31-41.)

Optionally, the dosage form can include one or more additional active ingredients suitable for the treatment of gastrointestinal disorders, for example heartburn, ulcers or diarrhea. Suitable active agents for treating gastrointestinal disorders include heartburn or antiulcer medicaments such as sucralfate, the H<sub>2</sub> receptor antagonists cimetidine, ranitidine, famotidine or nizatidine, proton pump inhibitors such as omeprazole or lansoprazole; antidiarrheal agents such as loperamide and diphenoxylate; gastrointestinal motility agents such as cisapride, and antacids such as aluminum hydroxide, magnesium carbonate, magnesium hydroxide, calcium carbonate and the like. The amount of such additional active ingredient combined with the simethicone should be an amount sufficient to provide a therapeutic dosage to a patient suffering from the gastrointestinal disorder being treated.

(Col. 5, Ins. 13-28.)

## EXAMPLE 1

### Preparation of Simethicone/Granular Anhydrous Tribasic Calcium Phosphate Admixture

1. 700 gm of granular tricalcium phosphate (Tritab®<sup>3</sup>, Rhone-Poulenc, Shelton, Conn.) is added to the mixing bowl of a Kitchen Aid mixer.

2. While mixing at low speed, over a period of 5 minutes add 200 gm of simethicone, USP.

3. Continue mixing at low speed for an additional 5 minutes.<sup>4</sup>

4. Add 2.5 gm of silicon dioxide and mix an additional 5 minutes.

This intermediate is a free flowing granulation with no large agglomerates.

(Col. 5, Ins. 31-

44.)

## EXAMPLE 2

### Preparation of Simethicone/Granular Anhydrous Dibasic Calcium Phosphate Admixture

- 1) 700 gm of granular anhydrous dibasic calcium phosphate, (Emcompress® Anhydrous, Mendell, Paterson, N.J.) is added to the mixing bowl of a Kitchen Aid mixer.
- 2) While mixing at low speed, over a period of 5 minutes add 200 gm of simethicone, USP.
- 3) Continue mixing at low speed for an additional 5 minutes.
- 4) Add 7.5 gm of silicon dioxide and mix an additional 5 minutes.

This intermediate is a free flowing granulation with no large agglomerates.

(Col. 5, Ins. 45-

59.)

## EXAMPLE 4

### Preparation of Chewable Tablets Containing Simethicone/Granular Anhydrous Tribasic Calcium Phosphate Admixture

- 1) 1500 gm of tricalcium phosphate powder was dry granulated by roller compacting at a roll pressure of 500 psi.
- 2) The compact was passed through a Fitz Mill with a 0.093" screen, knives forward.
- 3) The milled material was screened, and the -30 to +80 mesh fraction collected as product.
- 4) 700 gm of compacted tricalcium phosphate granules was added to the mixing bowl of a Kitchen Aid mixer.
- 5) While mixing at low speed, over a period of 5 minutes add 200 gm of simethicone, USP.
- 6) Continue mixing at low speed for an additional 5 minutes.
- 7) Add 20 gm of tricalcium phosphate powder and mix an additional 5 minutes.

This intermediate is a free flowing granulation with no large agglomerates.

- 8) 91 gm of the above intermediate was then blended with 98 gm of Dextrose, 7.5 gm granular sorbitol, 0.6 gm peppermint flavor, and 0.5 gm stearic acid.
- 9) The blend was finally compressed using  $\frac{5}{8}$ " FFBE tooling. The tablet weight was 1300 mg. The physical properties of the tablet were:

Hardness: 11-12 kp

Friability: less than 0.1% at 100 drops

Disintegration in N/10 HCl: less than 1.5 minute

Defoam: 7 secs

(Col. 6, Ins 28-58.)

## EXAMPLE 6

### Preparation of Swallowable Film Coated Tablets Containing Simethicone/Granular Anhydrous Tribasic Calcium Phosphate Admixture

| Ingredient   | Qty mg/tab |
|--|------------|
| <u>PART I - concentrate</u>                            |            |
| Tribasic calcium phosphate, NF,<br>Anhydrous, granular | 500        |
| Simethicone, USP                                       | 125        |
| Tribasic calcium phosphate, NF,<br>Anhydrous, Powder   | 25         |
| <u>PART II- Scavenger</u>                              |            |
| Tribasic calcium phosphate, NF,<br>Anhydrous, Powder   | 20         |
| <u>PART III- Excipient/Binder system</u>               |            |
| Dibasic calcium phosphate, Dihydrate,<br>USP           | 125.75     |
| Microcrystalline cellulose, NF (MCC)                   | 5.2        |
| Crystalline sorbitol, NF                               | 70         |
| Croscarmellose sodium, NF                              | 30         |
| <u>PART IV-Lubricant</u>                               |            |
| Magnesium Stearate, NF                                 | 0.5        |

PART 1) A concentrate comprised of granular and powdered anhydrous tribasic calcium phosphates, and simethicone is prepared by adding simethicone compound, USP to a moving bed of granular tribasic calcium phosphate so that the simethicone is distributed evenly and the granular calcium phosphate particle size remains essentially unchanged. The bed is kept in motion by low shear mixers such as fluid bed, Nauta, PK without intensifier bar, pin mixer, or ribbon mixer. After the bed has adsorbed the simethicone, anhydrous tribasic calcium phosphate powder is added. The granulation may then be screened through a No. 20 US Std screen (~840 micron).

PART 2) When a final blend for compression is desired an additional quantity of calcium phosphate powder is added to the PART 1 concentrate and blended.

**PART 3)** Excipients including a disintegrant are then added with low shear blending which imparts uniform distribution of the active within a binding matrix of limited compositional range.

**PART 4)** The final addition step is to add a lubricant.

**PART 5)** The blend is compressed into tablets using a rotary tablet press.

**PART 6)** Tablets are then film coated and/or gelatin dipped. Typical film coated tablet characteristics:

Hardness range: 6–14 kp

Tablet weight (core): Approx. 1000 mg

USP disintegration time in water : Less than 7 minutes, in acid media : Less than 6 minutes

USP Defoaming activity time: 9 seconds

(Col. 7, line 26 – col.

8, line 13.)

In making the rejection of claims 1-2 the Examiner asserted that “Luber teaches an antifoam oral solid dosage form preparations formed from a free [f]lowing granular composition comprising an admixture of simethicone and [] either one or both of granular anhydrous tribasic calcium phosphate or dibasic calcium phosphate, wherein the simethicone is adsorbed by the granular anhydrous tribasic or dibasic calcium phosphate or mixture thereof, and where ratios of simethicone to granular tricalcium phosphate are 1:3.5 in Examples 1-2 and 1:4 in Example 6. (OA at 6.) The Examiner further asserted “[a]lthough Luber is silent about the use of granular tribasic calcium phosphate or dibasic calcium phosphate as an adsorbent” such compounds “read[] on the broadly defined term “adsorbent.” Based upon this, the Examiner concluded that “the reference clearly anticipates the claimed invention” because “the claimed weight ratio of simethicone to adsorbent” encompasses the weight ratio of simethicone to tribasic calcium phosphate or dibasic calcium phosphate disclosed in Luber.

As is well settled, anticipation requires “identity of invention.” Each and every element recited in a claim must be found in a single prior art reference and arranged as in the claim.

The claimed ratios of simethicone to adsorbent were converted to their quotients in an attempt to aid the Examiner in understanding the instant invention. Using this ratio, it is clear that Luber does not disclose as much as the Examiner asserted. For example, the Examiner asserted that the ratios of simethicone to granular tricalcium phosphate

were 1:3.5 (0.28) in Examples 1-2 and 1:4 (0.25) in Example 6. It is submitted that a ratio of about 0.28 and 0.25 do not fall within the claimed ratio of at least about 0.45. For this reason, the rejection is improper and should be withdrawn.

Because claims 2, 4-5, 7-8, and 11-12 depend from claim 1 under the doctrine of claim differentiation, the rejection to these claims based on Luber is also improper and should be withdrawn.

In addition, the Examiner rejected claims 4-5, 7-8, and 11-12 in view Stevens. (OA at 7-8.) However, the instant rejection was not in view of Stevens, it was in view of Luber. For this additional reason, the rejection is improper and should be withdrawn.

#### **Obviousness Rejection**

Claims 3, 9-10, 13-15, and 19-26 were rejected under 35 USC §103(a) as being unpatentable over Kitsusho Yakuhin Kogyo KK (JP 398241) ("Kitsusho") in view of Tobyn et al, (International Journal of Pharmaceutics 169 (1998) 183-194) ("Tobyn") (OA at 9.)

For the reasons set forth below the rejection, respectfully is traversed.

Kitsusho discloses discloses a method for preparing simethicone tablets by mixing and granulating simethicone with aluminum silicate, magnesium aluminum metasilicate, and magnesium silicate. (p. 2.) In particular, the formulation disclosed by the above Japanese patent requires at most 25 % simethicone and 75% or greater silicate, binder and dispersing agent. Binders were disclosed as being starch and lactose. Dispersing agent was disclosed as being carboxymethylcellulose. Further, Kitsusho discloses that when the amount of simethicone exceeds 25%, a portion of the simethicone can be carried away, therefore the tablet workability is not desirable.

Tobyn discloses a comparison between microcrystalline cellulose ("MCC") and silicified microcrystalline cellulose ("siMCC"). According to Tobyn, MCC has properties such as low bulk density, high lubricant sensitivity, poor flow characteristics, and influence of moisture on the compression characteristics. (Tobyn at 183.) Tobyn disclosed that surface treatment of MCC with silicon dioxide or silicic acid had beneficial characteristics with respect to disintegration and mechanical resistance. (Tobin at 184.) Tobyn also discloses that siMCC was chosen to possess a number of pharmaceutical advantages in terms of powder flow, tablet strength, lubricant sensitivity and we

granulation. (Tobyn at 184.) Tobyn disclosed making a dry mix using Emcocel 90 M and dried silica and a wet mix was made using Emcocel 90 M with colloidal silica dispersion, which was tray dried and milled. (Tobyn at 184-85.) Tobyn concluded that no bulk chemical changes in MCC occurred with converted to siMCC. (Tobyn at 193.) Tobyn went on to postulate that “[t]he fundamental chemical properties of the novel material are very similar to the parent material.” (Tobyn at 193.) Tobyn also disclosed that siMCC had improved functionality in terms of improved bulk physical properties and mechanical characteristics due to some other intrinsic property rather than a change in the base chemical parameters of the novel material. (*Id.*)

In making the rejection, the Examiner asserted that Kitsusho teaches “teaches a method for preparing simethicone tablets by mixing and granulating simethicone with magnesium aluminum metasilicate. (OA at 9.) The Examiner further asserted that the “formulation disclosed by Kitsusho requires at most 25% simethicone and 75% or greater silicate, binder (i.e., starch and lactose) and dispersing agents (i.e., carboxymethylcellulose).” (OA at 9-10.) The Examiner also contended that “[Kitsusho] teaches that when the amount of simethicone exceeds 25% there is a tendency that a portion of the simethicone can be carried away, therefore the tablet workability is not desirable.” (OA at 10.) The Examiner acknowledged, however, that Kitsusho differs from the presently claimed invention in that:

1. the incorporation of silicified microcrystalline cellulose in said composition;
2. at least 30 wt% simethicone in said composition;
3. the specific amounts of silicified microcrystalline cellulose and magnesium aluminometasilicates in said composition; and
4. the specific har[d]ness of value of the tablet. (OA at 10.)

To fill the acknowledged gap, the Examiner relied upon Tobyn as disclosing the advantage of using silicified microcrystalline cellulose in improving tablet workability such as “powder flow,” “tablet strength,” “lubricant sensitivity” and “wet granulation.” (*Id.* at 10.)

The Examiner then concluded that “[t]o incorporate such teaching into the teaching of Kitsusho, would have been obvious in view of Tobyn, who teaches the

advantage of using silicified microcrystalline cellulose as a pharmaceutical excipient [] to improve powder flow characteristics, lubricant sensitivity, tablet strength and better bulk physical properties. (*Id.*) The Examiner reasoned that that “[o]ne having ordinary skill in the art would have been motivated, with a reasonable expectation of success, to incorporate silicified microcrystalline cellulose having good free-flowing and disintegrating properties (which is relatively new pharmaceutical excipients in the art) such that the table workability would be significantly improved. (*Id.*) The Examiner reasoned further “one having ordinary skill in the art would have been motivated to increase the amount of simethicone above 25% in the solid final blend for tableting by incorporating silicified microcrystalline cellulose in said composition.” (OA at 10-11.)

The Examiner then asserted that “[a]lthough the prior art references are silent about the specific dosage amounts of active ingredients and the hardness value of tablet, the optimization of [known] active and inactive ingredients in a composition or the determination of optimum hardness value of the tablet is well considered within the skill of the artisan, absent evidence to the contrary.”

Obviousness, cannot be based upon speculation. Nor can obviousness be based upon possibilities or probabilities. Obviousness **must** be based upon facts, “cold hard facts.” When a conclusion of obviousness is not based upon facts, it cannot stand.

“Determination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention.” ATD Corp. v. Lydall, Inc., 159 F.3d 534, 546, 48 USPQ2d 1321, 1329 (Fed. Cir. 1998). There must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources, to select particular elements, and to combine them as combined by the inventor. See Ruiz v. A.B. Chance Co., 234 F.3d 654, 665, 57 USPQ2d 1161, 1167 (Fed. Cir. 2000); ATD Corp., 159 F.3d at 546, 48 USPQ2d at 1329; Heidelberger Druckmaschinen AG v. Hantscho Commercial Prods., Inc., 21 F.3d 1068, 1072, 30 USPQ2d 1377, 1379 (Fed. Cir. 1994) (“When the patented invention is made by combining known components to achieve a new system, the prior art must provide a suggestion or motivation to make such a combination.”).

The rejection uses Tobyn to fill in the acknowledged gaps in Kitsusho, yet fails to point out where in Tobyn even one experiment using simethicone is disclosed. The rejection then summarily concludes that one having ordinary skill in the art would have been motivated to increase the amount of simethicone above 25% in the solid final blend for tabletting by incorporating silicified microcrystalline cellulose in said composition.

However, the rejection does not support such a conclusion. It is not seen where in the rejection the Examiner provided any facts in Tobyn to indicate that simethicone, a viscous oil-like substance, could be adsorbed onto silicified microcrystalline cellulose, much less any facts indicating that silicified microcrystalline cellulose would have the same improved properties when formulated with simethicone. Thus, the rejection is not supported by fact and must be withdrawn for this reason alone.

Further, the Examiner has not provided any facts to support the proposition that using siMCC in Kitsusho's formulation would overcome the problem acknowledged by Kitsusho, e.g., not exceeding 25% simethicone in the formulation. It is not seen where there are any facts in the rejection to suggest any expectation of success for increasing the amount of simethicone in a formulation using an additional adsorbent, e.g., siMCC. Because it appears that the rejection is based upon possibilities or probabilities, it is improper and should be withdrawn.

Claims 16 and 17 were rejected under 35 USC §103(a) as being unpatentable over Kitsusho in view of Tobyn and Stevens. (OA at 11.)

For the reasons set forth below the rejection, respectfully is traversed.

The disclosures of Kitsusho, Tobyn, and Stevens set forth above are herein incorporated by reference.

In making the rejection, the Examiner asserted that "the modified teach of Kitsusho includes all that is recited in claims 16 and 17 except for the incorporation of active pharmaceuticals such as famotidine. (OA at 11.) To fill the acknowledged gap, the Examiner relied on Stevens as "teach[ing] or suggest[ing] the use of simethicone and other pharmaceutical excipients in preparing oral solid dosage form containing H2 blockers (e.g., famotidine). (OA at 11.)

The Examiner contended that "[o]ne having ordinary skill in the art would have known that simethicone is routinely combined with H2 blockers such as famotidine in

solid oral dosage formulation art, and would have been further motivated to further modify the teaching of Kitshusho such that the better solid dosage form containing famotidine would be formulated. (OA at 11.) The Examiner reasoned “[o]ne having ordinary skill in the art would have been motivated to do this so that the tablet workability would be significantly improved.” (OA at 11.)

Obviousness, cannot be based upon speculation. Nor can obviousness be based upon possibilities or probabilities. Obviousness **must** be based upon facts, “cold hard facts.” When a conclusion of obviousness is not based upon facts, it cannot stand.

“Determination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention.” ATD Corp. v. Lydall, Inc., 159 F.3d 534, 546, 48 USPQ2d 1321, 1329 (Fed. Cir. 1998). There must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources, to select particular elements, and to combine them as combined by the inventor. See Ruiz v. A.B. Chance Co., 234 F.3d 654, 665, 57 USPQ2d 1161, 1167 (Fed. Cir. 2000); ATD Corp., 159 F.3d at 546, 48 USPQ2d at 1329; Heidelberger Druckmaschinen AG v. Hantscho Commercial Prods., Inc., 21 F.3d 1068, 1072, 30 USPQ2d 1377, 1379 (Fed. Cir. 1994) (“When the patented invention is made by combining known components to achieve a new system, the prior art must provide a suggestion or motivation to make such a combination.”).

The rejection uses Tobyn to fill in the acknowledged gaps in Kitsusho, yet fails to point out where in Tobyn even one experiment using simethicone is disclosed. The rejection then summarily concludes that one having ordinary skill in the art would have been motivated to increase the amount of simethicone above 25% in the solid final blend for tableting by incorporating silicified microcrystalline cellulose in said composition.

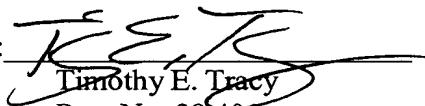
However, the rejection does not support such a conclusion. It is not seen where in the rejection the Examiner provided any facts in Tobyn to indicate that simethicone, a viscous oil-like substance, could be adsorbed onto silicified microcrystalline cellulose, much less any facts indicating that silicified microcrystalline cellulose would have the same improved properties when formulated with simethicone. Thus, the rejection is not supported by fact and must be withdrawn for this reason alone.

Further, the Examiner has not provided any facts to support the proposition that using siMCC in Kitsusho's formulation would overcome the problem acknowledged by Kitsusho, e.g., not exceeding 25% simethicone in the formulation. It is not seen where there are any facts in the rejection to suggest any expectation of success for increasing the amount of simethicone in a formulation using an additional adsorbent, e.g., siMCC. Because it appears that the rejection is based upon possibilities or probabilities, it is improper and should be withdrawn.

Finally, Stevens does appear to close the gaps in the Examiner's rejection. The sole example in Stevens relied on by the Examiner provides factual evidence that the ratio of simethicone to adsorbent (dibasic calcium phosphate + microcrystalline cellulose + colloidal silicon dioxide) is 125:667, which is about 0.19. It is submitted that a ratio of about 0.19 does not fall within the claimed ratio of at least about 0.45. For this additional reason, the rejection is improper and should be withdrawn.

Accordingly, for the reasons set forth above, entry of the amendments, withdrawal of the rejections, and allowance of the claims is respectfully requested. If the Examiner has any questions regarding this paper, please contact the undersigned.

Respectfully submitted,

By:   
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**VERSION WITH MARKINGS TO SHOW CHANGES MADE  
IN THE SPECIFICATION**

The specification was amended as follows:

The abstract of the disclosure was amended as follows:

--The present invention provides a composition for forming a compressed solid dosage form that is a free-flowing compressible admixture of simethicone, an adsorbænt, and an optional active agent, wherein the weight ratio of simethicone to adsorbent is at least 1:2.22, or 0.45. Also included are solid dosage forms made from a free-flowing compressible admixture of simethicone, an adsorbænt, and an optional active agent, wherein the weight ratio of simethicone to adsorbent is at least 1:2.22, or 0.45--

The Summary of the Invention was replaced with the following rewritten paragraph:

--The present invention provides a composition for forming a compressed solid dosage form that is a free-flowing compressible admixture of simethicone, an adsorbænt, and an optional active agent, wherein the weight ratio of simethicone to adsorbent is at least about 1:2.22, or 0.45. Also included are solid dosage forms made from a free-flowing compressible admixture of simethicone, an adsorbænt, and an optional active agent, wherein the weight ratio of simethicone to adsorbent is at least about 1:2.22, or 0.45--

Paragraph 16 was replaced with the following rewritten paragraph:

--Examples of suitable active agents include stimulant laxatives, such as bisacodyl, cascara sagrada, danthron, senna, phenolphthalein, aloe, castor oil, ricinoleic acid,, and dehydrocholic acid, and mixtures thereof; antisecretory; H<sub>2</sub> receptor antagonists, such as famotaidine, which is commercially available from McNeil-PPC, Inc. under the PEPCID brand; proton pump inhibitors; gastrointestinal cytoprotectives, such as sucralfate and misoprostol; gastrointestinal prokinetics, such as Prucalopride, antibiotics for *H. pylori*, such as clarithromycin, amoxicillin, tetracycline, and

metronidazole; antidiarrheals, such as diphenoxylate and loperamide, which is commercially available from McNeil-PPC, Inc. under the IMMODIUM brand; glycopyrrolate, such as Robinul; antiemetics, such as Ondansetron, analgesics, such as mesalamine, commercially available under the ASACOL brand, aspirin, and salicylic acid; and mixtures thereof.--

Paragraph 17 was replaced with the following rewritten paragraph:

--In one embodiment, the additional active agent may be selected from bisacodyl, famotidine, prucalopride, diphenoxylate, loperamide, lactase, mesalamine, bismuth, and pharmaceutically acceptable salts, esters, isomers, and mixtures thereof.--

Paragraph 26 was replaced with the following rewritten paragraph:

--As used herein, the term "adsorbænt" means a solid material or combination of solid materials that is capable of adsorbing and carrying an oily or fluid material, such as simethicone, while retaining sufficient flowability to assure content uniformity and sufficient compactability to be processed into tablets using direct compression methods

Paragraph 32 was replaced with the following rewritten paragraph

--The weight ratio of simethicone to total adsorbænt (e.g. magnesium aluminometasilicate and silicified microcrystalline cellulose) is at least about 1:2.22, or 0.45, for example at least about 1:2.00, or 0.50, or at least about 1:1.80, 0.56. In one embodiment, the weight ratio of simethicone to total adsorbænt is at least about 1 part simethicone to 1.75 parts adsorbænt, or about 0.57.--

### In the Claims

Claim 1 was amended as follows:

1. (Amended) A composition for forming a compressed solid dosage form comprising a free-flowing compressible admixture of simethicone and an adsorbænt, wherein the weight ratio of simethicone to adsorbænt is at least about 0.45 1:2.22.

Claim 2 was amended as follows:

2. (Amended) A composition of claim 1, wherein the weight ratio of simethicone to adsorbænt is at least about 0.50 1:2.00.

Claim 3 was amended as follows:

3. (Amended) A composition of claim 1, wherein the adsorbent comprises a combination of silicified microcrystalline cellulose and magnesium aluminometasilicate.

Claim 5 was amended as follows:

5. (Amended) A composition of claim 4, wherein the active agent is selected from the group consisting of bisacodyl, famotidine, prucalopride, diphenoxylate, loperamide, lactase, mesalamine, bismuth, and pharmaceutically acceptable salts, esters, isomers, and mixtures thereof.

Claim 9 was amended as follows:

9. (Amended) A composition of claim 13 having from about 19 wt% to about 27 wt% silicified microcrystalline cellulose and having from about 31 wt% to about 39 wt% magnesium aluminometasilicate.

Claim 14 was amended as follows:

14. (Amended) A solid oral dosage form of claim 13, wherein the weight ratio of simethicone to silicified microcrystalline cellulose and magnesium aluminometasilicate adsorbent is at least about 0.501:2.00.

Claim 17 was amended as follows:

17. (Amended) A solid oral dosage form of claim 16, wherein the active agent is selected from the group consisting of bisacodyl, famotidine, prucalopride, diphenoxylate, loperamide, lactase, mesalamine, bismuth, and pharmaceutically acceptable salts, esters, isomers, and mixtures thereof.

Claim 23 was amended as follows:

23. (Amended) A solid oral dosage form of claim 13, wherein the compressed admixture composition is compressed into a tablet having a hardness value of at least 2 kp/cm<sup>2</sup>.

Please amend claim 24 as follows:

24. (Amended) A solid oral dosage form of claim 13, wherein the compressed admixture composition is compressed into a tablet having a hardness value of from about 5 to about 10 kp/cm<sup>2</sup>

Claim 26 was amended as follows:

26. (Amended) A compressed solid dosage form comprising an admixture of simethicone, silicified microcrystalline cellulose, magnesium aluminometasilicate,

wherein the weight ratio of simethicone to silicified microcrystalline cellulose and magnesium aluminometasilicate adsorbent is at least about 0.501:2.00.